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August 22, 2000

Gil R. Gonzales, M.D.
G & P Technologies, Inc.
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New York New York 10021

Re: U.S. Patent Application
COMBINATION AND METHOD INCLUDING A VISUAL MARKER FOR DETERMINING COMPLIANCE WITH A THERAPEUTIC DRUG REGIMEN
Our Ref: UNSP-04

Dear Gil:

Please find enclosed a first draft of the above-referenced patent application. Please review the patent application for content and accuracy. I have left several "Notes" in the application where further information or details would be desired.

Specifically, we are claiming invention as the combination of an orally administered medication and a marker, where the marker is present in the combination in a form and sufficient amount to cause discoloration of at least a portion of the oral cavity. To that end, it would be helpful if we could say a specific amount that would be utilized. For example, one form of the marker in an embodiment comprises a coating placed on a pill or tablet. It would be helpful if we could say a range of thicknesses for such a coating which would be suitable. Furthermore, in one embodiment of the invention, we claim a marker that has a half life which is comparable to the half life of the medication composition in the human system. Do we have any examples of such a half life, or an example of a medication/marker combination?

After you have had a chance to review the application, please call me with your comments and revisions so that we may place the application in a more finalized form.

Very truly yours,

Kurt A. Summe

KAS:jra
Enclosures
cc: Thomas B. Jennings, Esq. (via fax)

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DATE: August 22, 2000

RE: UNSP-04

TO: Mr. Thomas B. Jennings

FROM: Kurt A. Summe

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If transmission is interrupted or of poor quality, please notify us immediately by calling (513) 241-2324 and ask for Janet Andrews. OUR FAX NUMBER IS (513) 421-7269.

resent 8/23

EXPRESS MAIL NO.: _____

PATENT APPLICATION FOR UNITED STATES PATENT

Title: COMBINATION AND METHOD INCLUDING A VISUAL MARKER FOR DETERMINING COMPLIANCE WITH A THERAPEUTIC DRUG REGIMEN

Applicant(s): Gilbert R. Gonzales, M.D.

Attorney Docket No.: UNSP-04

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SPECIFICATION

Abstract

A method and combination including a visual marker for monitoring a patient to determine compliance with a medication regimen. An orally administrable medication composition is provided in combination with a visual marker. When the combination is orally ingested, the marker causes a discoloration of the oral cavity of a subject. By visually observing the oral cavity of the subject, one can determine wether medication has been ingested due to the presence or absence of the discoloration.

Field of Invention

The present invention relates generally to monitoring therapeutic drug ingestion, and more particularly to a method and composition used for monitoring a patient to determine compliance by the patient with a medication regimen.

Background of the Invention

The term "compliance" in the practice of medicine, and specifically in pharmacotherapy, is defined as the "extent to which the patient's behavior coincides with the clinical prescription" (Litt, I.F. and Chuskey, W.R., *Compliance with medical regimens during adolescence*, Pediatric Clin North Am, 27:3, 1980).

When selecting a medication for a specific patient, many factors are considered, including the medication's efficacy profile, safety profile, route of administration, price, and the compliance of the patient in taking the medication. If a medication must be taken more than once a day, compliance becomes the most important factor in selecting a drug because the pharmacologic efficacy of the medication will be more adversely affected if the medication is not taken as directed. The problem of noncompliance with a prescribed regimen has become so serious

that, in response to such a problem, the pharmaceutical industry has developed long-acting forms of many medications.

The problems with noncompliance are particularly pronounced among certain groups of patients. These groups include: (1) pediatric patients, particularly those in child care centers or schools where medications are to be delivered by caregivers or teachers; (2) geriatric patients, whose caregivers are present only intermittently; (3) mentally handicapped individuals, who live independently or whose caregivers are present only intermittently; and (4) disease or disorder specific groups, including patients suffering from alcohol dependence, drug dependence, seizures, certain psychiatric conditions, cardiovascular disease, hypertension, or other conditions.

Accordingly, noncompliance is a problem that is widespread in society. Research has shown that patients only ingest half of the medication that is actually prescribed by physicians (Haynes, R.B., Taylor, D.W., and Sackett, D.L., Compliance in Health Care, Johns Hopkins University Press, Baltimore, 1979). Other studies have shown that up to 93% of medication regimens are not followed as prescribed (Greenberg, R.N., *Overview of patient compliance with medication dosing: A literature review*, Clin Ther, 6:592-599, 1984). The proportion of those that do not ingest their prescribed medication is greatest when social and cultural barriers, such as a language difficulty, exist, or when a decline in cognitive understanding, such as memory loss, interferes with carrying out instructions. Also, compliance varies with the illness that is treated, the degree of distress associated with symptoms, the complexity of the dosing regimen, the duration of the disease, and the extent of the adverse effects (Del Boca, F.K., Kranzler, H.R., Brown, J., and

Korner, P.F., *Assessment of medication compliance in alcoholics through UV light detection of a riboflavin tracer*, Alcohol Clin Exp Res, 20(8):1412-1417, 1996; Babiker, I.E., Cooke, P.R., and Gillett, M.G., *How useful is riboflavin as a tracer of medication compliance?*, J Behav Med, 12:25-38, 1989).

Therefore, noncompliance is a major problem in medicine in general, and in several diseases in particular. As an example, schizophrenia is associated with a noncompliance rate of 11 to 50% with an average of 33% (Maarjberg, K., Aagaard, J., and Vestergard, P., *Adherence to lithium prophylaxis: 1. Clinical predictors and patient's reasons for non adherence*, Pharmacopsychiatry 21:121-125, 1988; Kane, J.M. and Borenstein, M., *Compliance in long-term treatment of schizophrenia*, Psychopharmacol Bull, 21:23-27, 1985; Van Putten, T., *Why do schizophrenic patients refuse to take their drugs?*, Arch Gen Psychiatry, 31:67-72, 1974; Babiker, I.E., *Noncompliance in schizophrenia*, Psychiat Dev, 4:329-337, 1986). As a result, multiple areas of medicine have been subject to extensive and specific methodologic testing for compliance. One example of a relatively easy testing method, the use of riboflavin fluorescence in the urine, has been used for testing compliance under many conditions and for many diseases. These include schizophrenia, clinical drug trials, alcohol dependence, iron deficiency, tricylic antidepressant therapy, hypertension medication, the use of oral contraceptives in adolescents, anti-epileptic drug use, and cardiovascular diseases (Babiker, et al., *How useful is riboflavin as a tracer of medication compliance?*, J Behav Med, 12:25-38, 1989; Anton, *New methodologies for pharmacological treatment for alcohol dependence*, Alcohol Clin Exp Res, 20(7 Suppl): 3A-9A, 1996; Cromer, et al., *Psychosocial determinants of compliance in adolescents with iron deficiency*, Am J Dis Child, 143(1):55-58, 1989; Gilmore, et

al., *A study of drug compliance, including the effect of a treatment card, in elderly patients following discharge home from hospital,* Aging (Milano), 1(2):153-158, 1989; Perel, *Compliance during tricyclic antidepressant therapy: pharmacokinetic and analytical issues,* Clin Chem, 34(5):881-887, 1988; Sullivan, et al., *Compliance among heavy alcohol users in clinical drug trials,* J Subst Abuse, 1(2):183-194, 1988-1989; Tinguely, et al., *Determination of compliance with riboflavin in an antidepressive therapy,* Arzneimittelforschung, 35(2):536-538, 1985; Durant, et al., *Influence of psychosocial factors on adolescent compliance with oral contraceptives,* J Adolesc Health Care, 5(1):1-6, 1984; Jay, et al., *Riboflavin, self-report, serum norethindrone. Comparison of their use as indicators of adolescent compliance with oral contraceptives,* Am J Dis Child, 138(1):70-73, 1984).

Current methods to determine medication regimen compliance include clinical observation of patients, and the analysis of their bodily excretions. One common method of monitoring patients for medication regimen compliance is clinical observation involving individual counseling and close personal supervision by physicians. For example, physicians may observe a patient for physiological signs and symptoms indicative of compliance or noncompliance. These signs and symptoms may include residual signs of illness. Alternatively, the patient may be interviewed regarding the degree of relief from the affliction. A physician might also evaluate physiological changes in the patient. Clinical observation, however, is time consuming and, therefore, expensive. Furthermore, it is dependent on the physician's subjective opinion, and therefore is subject to potential errors.

Other methods of obtaining compliance information include qualitative urine monitoring methods. One example is the standard laboratory

procedure known as enzyme-multiplied immunoassay (EMIT). Utilizing an arbitrary cutoff value, these methods provide the clinician with a simple positive or negative indication of the possible presence or absence of a parent drug or its metabolites in a patient's urine. Urine monitoring methods may also be used to provide a quantitative analysis of ingestion of medication. However, whether qualitative or quantitative, several drawbacks exist in these analytical methods.

First, these analytical methods and tests are time and labor-intensive, often requiring the use of complex equipment in the analysis, and thus are not particularly useful when the time period between medication dosages is short. Second, these methods generally require a trained technician to perform the analysis. Third, the analysis is often performed at a location remote to the site where the sample is obtained. Finally, the sample collection itself involves a heightened degree of intrusiveness for the patient. As a result, these methods are not amenable to a rapid, generally non-intrusive, on-site assessment of compliance.

In an attempt to ameliorate some of the above-discussed problems of the monitoring methods of the prior art, markers have been used to determine the presence of medication in the system of a subject. However, these methods still require that the urine or stool of a subject be examined by a trained professional to detect the presence of the marker. Thus, while reducing some of the time and complexity involved, these tests are still not useful as a "home" test, still require some heightened degree of time, labor and expense, and do nothing to reduce the intrusiveness experienced by the patient.

While providing useful information relative to patient status and treatment compliance, the clinical monitoring methods described above have distinct

drawbacks which limit their usefulness in determining compliance. Thus, it would be desirable to develop a monitoring method that is rapid, simple, and inexpensive. Furthermore, it would be desirable for such a test to be amenable to use in the home by laypersons. Finally, it would be desirable for such a test to be minimally intrusive to the patient.

Summary of the Invention

The present invention solves the problems and eliminates the drawbacks of compliance methods and compositions of the prior art as developed in the Background of the Invention Section above. It does so by providing an orally administrable medication composition in combination with a visual marker. The marker can be observed visually and is present in combination with the composition in a sufficient amount and in a distinct form to cause a discoloration of at least a portion of the oral cavity of a subject following ingestion of the medication and the marker by the subject. For example, in one embodiment, the marker may stain a portion of the buccal membrane. This marker may be included in the combination in many forms, such as mixed in with the composition in a pill, capsule, chewable tablet or liquid. In the alternative, the composition may be formed into a pill, capsule, or tablet with the marker subsequently coated on the outside of the composition.

In use, shortly after ingestion of the marked medication, inspection would be carried out by looking at the oral cavity with the naked eye for a color or stain that is characteristically evoked by the marker. After the passage of time following ingestion, (e.g., _____ minutes) the visually apparent color or stain would evanesce leaving no apparent coloring of a portion of the oral cavity.

scheduled ingestion, or if needed, delayed by hours after the scheduled ingestion. The verification occurs by visual inspection of the oral cavity immediately after the delivery under natural light or delayed by hours by inspection under fluorescent light.

By virtue of the foregoing, there is thus provided a method and combination composition for monitoring the compliance of a patient in following a medication regimen while reducing and/or eliminating the problems associated with monitoring methods of the prior art. The present invention reduces the time, effort, complexity, and intrusiveness of prior art monitoring methods. These and other objects and advantages of the present invention shall be apparent from the accompanying detailed description of the invention.

Detailed Description

The present invention comprises in combination an orally administrable medication composition and a marker. As described in the summary of the invention, the marker of the combination is visually observable, either directly with the naked eye, or through fluorescence, and is present in the combination in a sufficient amount and form as to cause a discoloration or staining of at least a portion of the oral cavity of a patient following ingestion of the combination of marker and medication. For example, the buccal membrane may be marked and/or the gums or tongue surface may also be marked. Other surfaces in the oral cavity might also be marked or stained.

More specifically, in a first embodiment of the present invention, carmine red dye is used as a marker in combination with an orally administrable medication composition. The carmine red dye provides a stain of a portion of the

oral cavity and is thus used to determine whether the combination has been orally administered. This determination occurs by visual inspection either shortly after a scheduled ingestion or following the passage of a substantial amount of time after the scheduled ingestion. The discoloration or stain caused by the carmine red dye marker can be viewed either directly with the naked eye under natural white light or by fluorescing the residue of the carmine red dye.

Carmine red dye is approved by the U.S. Food and Drug Administration as a color additive for use in human food with no restrictions, as a color additive in use in topical drugs, and in color additives for use in cosmetics. Therefore, it is one suitable marker in accordance with the present invention. It is a red or purplish-red pigment derived from cochineal beetle shells that are crushed. In addition to being visible with the naked eye, commercial carmine produces a strong reddish-orange fluorescence at an exciting light wave length in the range of 450 through 490 nanometers, or around 436 nanometers.

Additionally, the inventor is not aware of any reported embryotoxic effects of carmine in animal studies (Grant, et al., *Tetratogenicity and embrotoxicity study of carmine of cochineal in the rat*, Food Chem Toxicol, 25(12):913-917, 1987). Rare carmine dye allergies have been reported, however, overall, carmine is considered one of the most inert and safest food additives known and is used in medical procedures, as noted in several publications (Miller and Anderson, *Silent regurgitation in day case gynaecological patients*, Anaesthesia, 43(4):321-323, 1988; Read, et al., *Transit of a meal through the stomach, small intestine, and colon in normal subjects and its role in the pathogenesis of diarrhea*, Gastroenterology, 79(6);1276-1282, 1980; Higgs, et al., *Assessment of simple methods of measuring*

intestinal transit times in children with gastroenteritis, Gut, 16(6):458-461, 1975; Hallagan, et al., *The safety and regulatory status of food, drug and cosmetics colour additives exempt from certification,* Food Chem Toxicol, 33(6):515-528, 1995; Schmidt, *"Tagged" local anesthetic solution for transurethral surgery,* Urology, 34(5):305-306, 1989; Reece, et al., *Transabdominal needle embryofetoscopy: a new technique paving the way for early fetal therapy,* Obstet Gynecol, 84(4):305-306, 1994).

While carmine red dye is used as the marker in one embodiment of the invention, in alternate embodiments of the present invention, other dyes can be used as markers. Such dyes include, without limitation, indigo carmine, methylene blue, tartrazine, and laccaic acid. The dyes must be medically safe or approved and must provide a visually detectable discoloration, either by the naked eye or through fluorescence. Furthermore, the marker is present in the combination with medication in an amount and form to cause discoloration of the oral cavity.

The combination of medication and marker of the present invention may be formed into ingestable tablets, or pills by processes known in the art of pill manufacturing. Tablets may be formed either by direct compression of the medication composition and marker or by granulation of the components of the combination followed by compression. Pills may be formed by compressing powdered or granulated components of the combination into small diameter tablets. Alternatively, the combination may be provided in the form of a liquid. In this embodiment, both the medication composition and the marker are solubilized in a liquid medium where the marker is interspersed with the medication, it must be in such a form in the finished tablet, pill or liquid as to be exposed to the oral cavity for

causing the discoloration. For example, with a tablet or pill form, the carmine red dye may be exposed to the outer surface of the tablet or pill so that it directly contacts the tongue, buccal membrane, and other areas of the oral cavity. Alternatively, the tablet or pill may be chewable in order to expose more area of the oral cavity to the marker. Generally, exposure of the oral cavity to the marker will readily occur in the liquid form. Capsules, which include the combination inside, will generally pass through the readily visible area of the oral cavity before they dissolve. Therefore, in such a form, they may not be particularly desirable. However, the capsule may be suitable if it rapidly dissolves in the oral cavity.

In alternate embodiments of the present invention, the medication composition alone may first be formed into ingestable capsules, tablets, or pills by processes known in the art of pill manufacturing and an outer coating may then be applied which contains the marker. Capsules may be formed by filling capsules with the medication composition using conventional automatic filling equipment. Tablets may be formed either by direct compression of the medication composition or by granulation of the composition followed by compression. Pills may be formed by compressing the powdered or granulated medication composition into small diameter tablets, as discussed above. Following formation of the medication composition into capsules, tablets, or pills, the marker is then coated onto the exterior surface thereof fo that it is exposed to the oral cavity when ingested.

For example, in the first embodiment of the present invention, the medication composition is provided in capsule form and the capsule is covered with a coating of the carmine red dye. More specifically, the carmine red dye is added to the exterior surface of the capsule as a lacquer or coating by applying a plurality of

coats of the carmine red dye to the surface of the capsule by any conventional technique. The carmine red dye coated on the surface of the capsule is applied in an amount sufficient to cause a discoloration of the oral cavity of a patient ingesting the capsule. The dye should be of such a form as to not wash away if the medication is taken with a liquid, such as water. **[Note: Gil, do we have any amounts we could cite? Such as a thickness of a coating, for example. Furthermore, do we know anything about the form of a coating, such as a powder form or a hard shell?]**

However, while the discoloration of the oral cavity is necessary for determining compliance, it is important that the presence of the marker not outlast the period between medication doses. Otherwise, a discoloration of the oral cavity may exist when medication has not been ingested in compliance with a designated regimen. Such false positive results would reduce the accuracy of compliance testing by the combination and method of the present invention. Thus, in accordance with one aspect of the present invention, in order to ensure that the marker does not remain visible for a longer period of time than the pharmacological efficacy of the medication composition, a marker may be chosen wherein the half-life of the marker in the human system is comparable to the half-life of the medication composition in the human system. Of course, if the half life of the marker was approximately equal to the half life of the medication, that would be particularly desirable. **[Note: Gil, we could use some examples if you have any.]**

The present invention also provides a method for monitoring the compliance of a patient in following a medication regimen. In this method, a patient is provided with a combination of an orally administrable medication composition and a marker. As described above, the marker is present in the combination in an

amount which is sufficient to cause a discoloration of at least a portion of the oral cavity of the patient. Following a scheduled dosage, the oral cavity of the patient is then visually observed in order to determine the presence or absence of discoloration of the oral cavity.

More specifically, in a first embodiment of the method of the present invention, the marker present in the combination is carmine red dye. Also, the specific portion of the oral cavity being observed is the oral mucous membrane or buccal membrane. If the patient has actually ingested the combination of medication composition and marker in accordance with the principles of the present invention, then the mucous membrane will be stained with a color indicative of carmine red dye. By periodically observing the mucous membrane of the oral cavity for this discoloration, according to a determined regimen, one can determine whether a patient is following a medication regimen. Thus, if no discoloration is apparent upon observation of the oral cavity, a caregiver can either require that the patient take the proper dosage of medication, or, if refusal persists, the caregiver can alter the method of medication delivery.

Also, as described above, the oral cavity may be observed either under natural light or under fluorescent light. More particularly, in the method of the present invention, inspection may be carried out immediately following the time for scheduled ingestion by visually observing the oral cavity of the patient for a color that is characteristically invoked by the colored marker. This observation is carried out under natural light and with the naked eye. In the first embodiment of the present invention, for example, a reddish coloration would appear on a mucous membrane in the oral cavity of the patient. If a time lapse occurs between the time scheduled

for ingestion and the time of actual observation, the visually apparent color caused by the marker may evanesce, leaving no apparent coloring of the oral cavity. However, determination of ingestion of the medication composition and marker may still be obtained through fluorescence of the oral mucous membrane. In this embodiment of the method of the present invention, a flourescent light may be used to evoke a visually apparent emission of a color which is characteristic of the marker. In the first embodiment of the present invention, the reddish-orange residue left by carmine red dye would be observed. In order to observe the carmine red marker residue by fluorescence, an optimal exciting light is directed into the oral cavity of the patient. To fluoresce the residue of carmine red dye, as in the first embodiment of the present invention, the light is either a violet-blue light having a wavelength of about 435 nm or, more broadly, a blue light having a wavelength in a range of from about 450 nm to about 490 nm might be used. **[Note: It would seem that the entire range of 430-490 could be suitable. Correct?]**

While the present invention has been illustrated by the description of various embodiments thereof, and while these embodiments have been described in considerable detail, it is not the intention of the Applicant to restrict or in any way limit the scope of the appended claims to such detail. Additional advantages and modifications will readily appear to those skilled in the art. The invention in its broader aspects is therefore not limited to the specific details, representative combination and method, and illustrative examples shown and described. Accordingly, departures may be made from such details without departing from the spirit or scope of Applicant's general inventive concept.

WHAT IS CLAIMED IS:

Claims :

1. A method of monitoring the compliance of a patient in following a medication regimen, said method comprising the steps of:

providing in combination an orally administrable medication composition, which is part of a medication regimen, and a marker, said marker being present in said combination in a form and sufficient amount to cause a discoloration of at least a portion of the oral cavity of a subject following ingestion of said combination by said subject; and

visually observing the oral cavity of said subject to determine the presence or absence of said discoloration, to thereby determine whether said subject has ingested said combination in compliance with the medication regimen.

2. The method of claim 1 wherein visually observing the oral cavity of said subject to determine the presence or absence of discoloration further comprises the step of directing natural light into the oral cavity of said subject prior to observing the oral cavity of said subject in order to directly observe said discoloration.

3. The method of claim 1 wherein visually observing the oral cavity of said subject to determine the presence or absence of discoloration further comprises the step of directing an optimal exciting light into the oral cavity of said subject prior to observing the oral cavity of said subject in order to observe said discoloration through fluorescence.

4. The method of claim 3 wherein said optimal exciting light is a violet-blue light having a wavelength of about 436 nm.

5. The method of claim 3 wherein said optimal exciting light is a blue light having a wavelength in a range of from about 450 nm to about 490 nm.

6. The method of claim 1 wherein visually observing said oral cavity comprises visually observing a mucous membrane in said oral cavity.

7. The method of claim 1 wherein said marker is carmine red dye.

8. The method of claim 1 wherein said marker is selected from the group consisting of indigo carmine, methylene blue, tartrazine, and laccaic acid.

9. In combination:

an orally administrable medication composition; and

a marker, said marker being present in said combination in a sufficient amount and form to cause a discoloration of at least a portion of the oral cavity of a subject following ingestion of said combination by said subject;

whereby said discoloration of the oral cavity may be visually observed to thereby determine whether said subject has ingested said combination in compliance with a medication regimen.

10. The combination of claim 9 wherein said marker is applied to the outer surface of said composition.

11. The combination of claim 9 wherein said marker is interspersed throughout said composition.

12. The combination of claim 10 wherein the form of said composition is selected from the group consisting of a chewable tablet, a pill, a capsule, and a liquid.

13. The combination of claim 11 wherein the form of said composition is selected from the group consisting of a chewable tablet, a pill, a capsule, and a liquid.

14. The combination of claim 9 wherein said marker is operable to cause discoloration of a mucous membrane of said oral cavity.

15. The combination of claim 9 wherein the half-life of said marker in the human system is comparable to the half-life of said composition in the human system.

16. The combination of claim 1 wherein said marker is carmine red dye.

17. The combination of claim 1 wherein said marker is selected from the group consisting of indigo carmine, methylene blue, tartrazine, and laccaic acid.